THE SYNTHESIS OF AMIDINES

BY

ROBERT WILLIAM UPSON

B.S., University of Nebraska, 1937

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AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE SCHOOL OF THE UNIVERSITY
OF ILLINOIS, 1941

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ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to Professor Ralph L. Shriner for suggesting this work and for his guidance and encouragement during the course of these investigations.

This opportunity is also taken to express the author's indebtedness to the Röhm and Haas Company for a Research Assistantship for the year 1938-1939 and to Eli Lilly and Company for a Research Fellowship for the years 1939-1941.

THE SYNTHESIS OF AMIDINES

INTRODUCTION

One of the important synthetic antimalarial compounds in use today is 6-methoxy-8-(ω-diethylamino-α-methylbutyl)-aminoquinoline, known as plasmoquin. Other similar quinoline derivatives, with a $-NH-(CH_2)_nNEt_2$ chain in position 8, also show strong antimalarial action.

Recent work has shown that aliphatic diamidines, especially 1, 11-undecandiamidine, possess considerable antimalarial activity. It, therefore, seems likely that the replacement of the terminal diethylamino group in the $-NH-(CH_2)_nNEt_2$ chain on the quinoline nucleus by an amidine group would result in a substance of value in the treatment of malaria. It would also be desirable to test a series of polymethylene-*bis*-benzimidazoles for their pharmacological action, as compounds of this type can be considered as substituted diamidines.

Since amidines of these types have not been previously prepared, it was the purpose of the present investigation to synthesize representative compounds of both types.

EXPERIMENTAL AND DISCUSSION

γ-Iodobutyronitrile was prepared from γ-chlorobutyronitrile [1] in 56 to 70 per cent yields by the action of potassium iodide in acetone solution. ε-Bromocapronitrile, ζ-bromoenanthonitrile and ω-bromohendecanonitrile were prepared in 30 to 32 per cent yields from the corresponding dibromide by the action of potassium cyanide and potassium iodide with methanol as the solvent.[2]

The 8-aminoquinoline used was prepared by the method of Smith and Getz [3] and 6-methoxy-8-aminoquinoline was synthesized as follows: *p*-anisidine → *p*-acetanisidide [4] → *o*-nitro-*p*-acetanisidide [5] → *o*-nitro-*p*-anisidine [5] → 6-methoxy-8-nitroquinoline [3] → 6-methoxy-8-aminoquinoline.[3] The over-all yield of 6-methoxy-8-aminoquinoline from *p*-anisidine was 38 to 40 per cent.

The condensation of 8-aminoquinoline with γ-chlorobutyronitrile in the presence of anhydrous sodium carbonate gave 8-(γ-cyanopropylamino)-quinoline and the corresponding 6-methoxy derivative was obtained by condensing γ-iodobutyronitrile with 6-methoxy-8-aminoquinoline. Treatment of 8-aminoquinoline and 6-methoxy-8-aminoquinoline with ε-bromocapronitrile, ζ-bromoenanthonitrile and ω-bromohendecanonitrile in the presence of

anhydrous sodium carbonate and potassium iodide at temperatures varying from 95 to 135° gave the corresponding quinolylaminonitriles in 30 to 70 per cent yields.

The quinolylaminonitriles were converted to the corresponding imino ethers[6] by the action of dry hydrogen chloride and absolute ethanol at a temperature of 0-10°. The imino ether hydrochlorides were hygroscopic and, therefore, were not isolated. Treatment of the imino ethers with a saturated solution of dry ammonia in absolute ethanol at room temperature yielded the corresponding amidines[6] which were isolated as their dihydrochloride salts. The over-all yield of the amidine from the corresponding nitrile was 75 to 95 per cent. Potentiometric titration of these salts indicated that the monohydrochlorides give neutral aqueous solutions. The dihydrochloride salts were colored and absorption spectra curves, in the visible range, were obtained for these compounds.

Treatment of the amidine dihydrochloride salts with a dilute solution of sodium hydroxide at room temperature gave the corresponding amide. As a check on the structure of these amides, ϵ-(8-quinolylamino)-caproamide was synthesized by the following sequence: 8-aminoquinoline + ϵ-bromocaproic acid → ϵ-(8-quinolylamino)-caproic acid → methyl ϵ-(8-quinolylamino)-caprate → ϵ-(8-quinolylamino)-caproamide. A mixed melting point with the amide obtained by treating ϵ-(8-quinolylamino)-caproamidine dihydrochloride with dilute alkali showed no depression.

The general method of Brown and Campbell[7] was used to prepare a series of polymethylene-*bis*-benzimidazoles. *o*-Phenylenediamine was condensed with succinic, glutaric, adipic, pimelic, suberic, azelaic and sebacic acids in the presence of 4 *N* hydrochloric acid and at a temperature of 125-135°. Both the free base and the dihydrochloride salt were white crystalline compounds having high decomposition points. The solubility and decomposition points of the dihydrochloride salts paralleled the solubility and melting points of the corresponding dibasic acids. The condensation of *o*-phenylenediamine with oxalic acid gave 2,3-dihydroxyquinoxaline, the structure of which was proved by conversion to 2,3-dichloroquinoxaline.[8] Malonic acid reacted with *o*-phenylenediamine to give a product with an empirical formula of $C_9H_8O_2N_2$, which appeared to be a polyamide type of polymer.

SUMMARY

6-Methoxy-8-aminoquinoline was synthesized as follows: *p*-anisidine → *p*-acetanisidide → *o*-nitro-*p*-acetanisidide → *o*-nitro-*p*-anisidine → 6-methoxy-8-nitroquinoline → 6-methoxy-8-aminoquinoline.

γ-Iodobutyronitrile was prepared from γ-chlorobutyronitrile and ε-bromocapronitrile, ζ-bromoenanthonitrile and ω-bromohendecanonitrile were prepared from the corresponding dibromide. The treatment of 6-methoxy-8-aminoquinoline and 8-aminoquinoline with these nitriles yielded the corresponding quinolylaminonitriles which were converted to the amidines by way of the imino ethers. Potentiometric titration curves and absorption spectra curves were obtained for each amidine dihydrochloride.

The condensation of *o*-phenylenediamine with succinic, glutaric, adipic, pimelic, suberic, azelaic and sebacic acids yielded the corresponding polymethylene-*bis*-benzimidazole while oxalic acid gave 2,3-dihydroxyquinoxaline and malonic acid gave a polyamide.

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VITA

The author was born near Odell, Nebraska, August 7, 1913. He attended a rural school near Odell and was graduated from Odell High School in 1930. The degree of Bachelor of Science in Chemistry was received from the University of Nebraska in 1937 and the degree of Master of Science in 1938. The author held an Avery Memorial Fellowship during the term 1937-1938. In September, 1938, he enrolled in the Graduate School of the University of Illinois, and held a Röhm and Haas Research Assistantship during 1938-1939 and an Eli Lilly Research Fellowship during 1939-1941.